TO: Drs. Meiklejohn, Thompson and Washburn, a Special Committee of the Faculty
FROM: Dr. Roger S. Mitchell

SUBJECT: A possible Department (or Division) of Genetics at the School of Medicine

I. Background:

In searching for outstanding research talent, the Colorado Foundation for Research in Tuberculosis became interested in Dr. Joshua Lederberg, Professor of Genetics, University of Wisconsin. The possibility of a Department or Division of Genetics in our school, concerned with both research and teaching and sponsored and housed by the Colorado Foundation for Research in Tuberculosis, has emerged from conversations and correspondence with Dr. Lederberg.

II. The general place of Genetics in a Medical School:

Public discussion of genetic hazards of exposure to radiation has focused renewed attention on the genetic factor in medicine; the level of this discussion helps to emphasize not only the gaps in our scientific knowledge but also in the effectiveness with which the knowledge we have gained has penetrated to the profession and to the lay public alike. The attitude of misunderstanding or mystery that often attaches to genetic issues may be contrasted with the familiarity with basic physiological and biochemical science that is a workaday tool of every well trained clinician. Inevitably, both genetic research and medical practice must suffer from this lack of rapport, where it pertains.

There are several signs of a new direction and emphasis on medical genetics today, however. For example, several excellent texts have, for the first time, appeared (Stern; Harris; Neel and Schull; Sorsby) and a number of medical schools (notably Michigan, Oklahoma, Minnesota, Utah, Bowman-Gray) are sponsoring research, teaching and clinics in this field. This reemphasis may be ascribed partly to the natural growth and differentiation of the medical sciences, partly to the popular interest in genetic hygiene, and perhaps significantly to the increasing relative importance of "constitutional" diseases as medical practice achieves effective control over contagious afflictions.

The introduction of a medical genetics center does not necessitate a separate department; this is a decision that will depend on many local and personal considerations. For the demands of clinical practice, it appears that highly specialized training in research methods is relatively unimportant, and the role of genetic etiology might be effectively integrated into all clinical teaching. But the same might be said of other basic sciences. Experiments with integrated teaching are under way; their success may well depend on the availability of integrated teachers, and until they have been trained themselves, differentiated departments and courses may be an unavoidable compromise.

The effectiveness of the teaching of genetics in a Medical School would depend a great deal on effective collaboration with the clinical departments

in the joint study of specific cases, wherever feasible. This collaboration should, ideally, extend beyond the classroom; the medical genetics staff should serve as a focus of consultation and provocation of interest in genetic aspects of diagnosis and therapy among the working faculty, a role that is possibly more critical than classroom teaching. To accomplish this effectively, the geneticist should be, on the one hand, well acquainted with the literature in the various fields of medical genetics, and on the other, conversant with the day to day problems of his clinical colleagues, and effective in linking the two.

At a university where research in various aspects of genetics is soundly developed, the clinical geneticist may be the only new staff appointment required to round out a genetics program. Elsewhere, a base may have to be built up gradually if a high quality of research and graduate education is to be anticipated. In such a circumstance, whether to start with the "clinical geneticist" or the basic research group is open to debate. A compromise might be effected if an M.D. or Ph.D. can be found who can combine both roles, at least for the time being.

III. A proposed course in Medical Genetics, suitable for the second or third year curriculum:

A. What is heredity

1. Twins. Nature and nurture.
2. Collection and interpretation of family data. Consanguinity analysis. Pedigrees. Single factor inheritance. Dominance. Sex linkage.
3. The chromosomes of man. Sex determination.

B. Common hereditary factors

4-5. Blood groups. Transfusion. Hemorrhagic disease of newborn. Forensic.
6. The hemoglobins and hereditary anemias.

C. Rare mutants in man.

7. Mutation. Metabolic diseases with physiological genetics Neurospora, etc., as background. Phenylketonuric oligophrenia; alkaptonuria; tyrosinosis.
8. Metabolic diseases continued: glycogen storage disease; galactosemic hepatomegaly; agammaglobulinemia; hemophilias. Metabolic individuality.

D. Polygenic inheritance

9. Genetic factors in infectious and constitutional disease; cancer.
10. Genetic factors in mental disease.

E. Genetic hygiene.

11. Aims and fallacies of eugenics; social and "industrial" medical problems from radiation (and chemicals?).

F. Experimental genetic studies on mammals.

12. Example--histocompatibility and acquired tolerance; the antibody response.

G. Microbial genetics.

13. Mutation studies. Drug resistance.
14. Recombination mechanisms.
15. Viruses (as organisms and as genes).

Some of these topics may already be adequately covered in other course work. Every effort should be made to correlate this with other offerings. It will be essential to seek the cooperation of clinical specialists 1) for appropriate case demonstrations, and 2) to ensure a balanced account of such topics as mental disease, eugenics and radiation hazards. If there are pronounced differences of opinion within the medical faculty, it may be profitable to arrange for joint presentations or discussions.

Student laboratory exercises would pose many problems, but might be worked out in collaboration with other courses (clinical pathology; physiological chemistry; microbiology).

It would be helpful to have some standardization of preparation in genetics. If many premedical students will already have included a course, it would be wise to urge most of them to do so; if not, more emphasis may be needed on the blood groups.

The course is not designed to indoctrinate specialists, but to inculcate an appreciation for the role of the genetic factor in the determination of disease and of normal personal individuality. With this background, the student may be better equipped to learn from his experience in the clinical years and his practice.

Text: Possibly "Harris-Introduction to Human Biochemical Genetics"

Reference Books: Sorsby-Clinical Genetics; Neel and Shull-Human Heredity; Stern-Human Genetics.

IV. <u>A general outline of genetic research related in whole or in part to Medicine</u>:

A. HUMAN GENETICS

1. Hereditary factors in disease

Statistical methodology. Pedigree analysis. Population analysis.
Twin studies.
Clinical genetics
  Single factor syndromes (e.g., hemophilia; retinoblastoma; xeroderma pigmentation)
  Complex determination (e.g., epilepsy; diabetes)
Biochemical or developmental analysis of genetic defects (e.g., alkaptonuria or phenylpyruvic oligophrenia; sickle cell anemia)
Mutation rates.

2. Individuality

   Blood groups
   Transplantation specificity
   Sensory modalities (e.g. phenylthiourea tests)
   Metabolic individuality[1]
   Antibody response[2]
   Anthropometry: skin and hair; features; 'race'
3. Cytogenetics
4. Genetic Hygiene and population genetics
   Eugenics[3]
   Counselling[4]
   Environmental medicine[5]
   Detection of heterozygous carriers

B. EXPERIMENTAL MAMMALIAN GENETICS

1. Mutation and radiation effects
2. Cytogenetics
3. Developmental analysis of gene effects
4. Biochemical analysis of gene effects
5. Experimental evolution
6. Transplantation—histocompatibility and acquired tolerance[6]
7. Susceptibility to infectious disease
8. Cancer Research—host variations and genetics of tissue and tumor cells[7].

C. MICROORGANISMS

Mutation. Radiation effects. Chemical mutagenesis. Mechanisms of killing cells.
Evolutionary patterns in natural populations (esp. of pathogens).
Genetic factors in pathogenicity.
Genetic recombination analysis.
Nature and origin of viruses.

Footnotes to IV: [1]This is readily recognised in characteristic metabolic disease but may be equally important in personal differences, as Roger Williams has emphasised. Individuality may thus be reflected in characteristic patterns of excretion of various metabolites and has a large, certainly not an exclusive, genetic basis. It is also reflected in differences in therapeutic response, e.g., to isoniazid, and may be a neglected factor in idiosyncratic responses to other drugs. Explicit genetic analysis of the latter situations remains to be carried out.

[2]For example, in the polio vaccination program, it has been noted that some children make a poor antibody response. It is not known whether this has a genetic basis, nor whether this is a general unresponsiveness or a specific unreactiveness to the polio virus. Fink (at Colombo) and others have given experimental evidence for genetic variability in antibody response in mice. This field should be one of the more important areas of development for practical medical understanding. The general question of individualized reactions to pathogens is not far distant.

[3]Exaggerated emphasis on "eugenic" programs for the sterilization of the so called "unfit" is largely responsible for the hindered development of

medical genetics. Such negative controls are essentially futile for the reduction in incidence of rare recessive mutations in any event, and involve matters of public policy that far overreach the authority of the medical profession per se. Many modern students (cf. Neel and Shull) share the view that much more scientific knowledge of human genetics is needed before one can advocate any far reaching social controls of human reproduction. The present role of the human geneticist is to inform his colleagues in medical practice and through them the public, rather than advocate drastic interference by society, especially when the calculated social effects are so small. On the other hand, the public is entitled to have access to physicians who can intelligently advise their patients on genetic problems.

Medicine may someday be faced with formulating an attitude on another issue where genetic control may be more effective, namely the sex ratio. This has not been the subject of much work lately, but it is at least theoretically possible that techniques will ultimately be developed to enable the sex of offspring to be voluntarily controlled. Most of us would hope that day to be deferred indefinitely, but this illustrates the tremendous impact that human genetics is bound to have, ultimately, on medicine and on society.

4Counselling. Many schools have set up "Heredity Clinics" as part of their program in medical genetics. These are valuable centers for the collection of data, and there can be no question of public interest in these problems. Such a service in which the genetic specialist deals directly with the patient is not advocated. The counsellor inevitably must influence the patient's reproductive decisions, matters so involved with his total personality that such consultation should ordinarily be made with his own physician. The department should be in a position to consult with physicians, and inevitably will.

5"Environmental medicine" is taken here to encompass the genetic hazards from industrial and professional operations, as well as from atomic bombs. Almost all the emphasis so far has been spent on radiations (from bombs, fluoroscopy or mineral extraction), and, except that some hazard is involved, little enough is known. Without minimizing the tremendous importance of radiation hazards from, for example, fallout, it seems there is a much broader problem of which radiation is only one part. Until recently, radiations were considered the only artificial agency by which mutations could be induced. It is now realised that a wide variety of chemical reagents can induce mutations. Radiations undoubtedly have freer access to the germ cells, but the mutagenicity of such compounds as hydrogen peroxide, formaldehyde, nitrogen mustard, azaserine, and caffeine raises the question whether genetic effects should be considered as one aspect of chronic toxicity of compounds which are part of the everyday environment of modern man.

6Experimental studies have now firmly established the immunogenetic basis of transplantation compatibility in mammals. It is disheartening to see how often these factors are ignored in surgical reports. Prenatal exposure of mice to heterologous tissue antigens provokes a tolerence to the postnatal transplantation of similar tissues. This is an important lead to the development of techniques for overcoming histocompatibility barriers which hinder the potentially vast applications of organ replacement. These studies also promise to give answers to one of the mysterious questions of immunology: why does the organism fail to produce antibodies to its own antigens?

7Most of the emphasis in genetic cancer research has been in the properties of specific lines of mice, which are indeed indispensable research tools.

More recently, technical advances are leading to closer examination of the genetics of the tissue cell itself, as in the ascites tumor studies of Hauschka and Klein, and the extremely promising tissue culture findings of Puck.

V. Specific considerations on possible interrelations between the University of Colorado School of Medicine, the Colorado Foundation for Research in Tuberculosis and Dr. Joshua Lederberg.

1. The Foundation: the Foundation charter directs the pursuit of medical research with special emphasis on tuberculosis. Our chief interest still remains in tuberculosis. Well established first class tuberculosis researchers are very limited in number and appear to be unavailable to us so far. The Trustees as a consequence have agreed to go out of the field of tuberculosis research, if necessary, in order to secure first class research ability; i.e. the quality of research is considered more important than the subject.

2. The School: The creation of a Department of Genetics in the School, supported largely or even entirely by the Foundation, would be a new departure on at least two counts:

a) An increase rather than a further decrease in the number of departments or divisions of the School.
b) The new emphasis on the subject of genetics.

3. Dr. Lederberg: There is no question that this whole matter has come up now because of the possible availability of a scientist of Dr. Lederberg's caliber. (He is responsible incidentally, for the information contained in sections II, III, IV and VI). He will not be available, if at all, for from one to three years. He would bring with him his wife who is also an accomplished microbial geneticist.

His curriculum vitae follows: He was born in Montclair, New Jersey in 1925. He received his B.S. degree from Columbia in 1944 and his Ph.D. from Yale in 1946. He came to the University of Wisconsin as Assistant Professor of Genetics in the College of Agriculture in 1947. He had risen to the rank of full Professor by 1953. He received the Eli Lilly award in 1953 for outstanding work by a scientist under 35 years of age.

He has published over 50 papers on microbial genetics, a list of which is available for those interested. Among his outstanding contributions are the demonstration of sex in bacteria and the clear demonstration that bacterial resistance to chemotherapeutic agents is due to mutation rather than adaptation.

Dr. Lederberg would not want to come here without considerable autonomy in planning his research and teaching, hence the suggestion of a new Department. A division of a present department (e.g., Medicine) might well meet the needs of the situation after further consideration and discussion.

VI. Growth of a Department (or Division) of Genetics.

If this proposal is initiated with a staff of two or three microbial geneticists, workers (at least part time) in mammalian genetics and in clinical genetics would soon be desirable, especially the former. Because of the interrelated problems, some affiliation with the Blood Bank might be a logical development.

VII. Summary

Presented here for the consideration of those Medical School and University officials concerned is a proposal for the creation of a new program of teaching and research in Genetics at the Medical School. It revolves particularly around one man, Dr. Joshua Lederberg, whose thinking is responsible for the plan presented. It is definitely exploratory at this point. More detailed information on the subject can be obtained from the writer if desired. Before going further, the Foundation desires some official reaction from the authorities of the School and University.

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in Tuberculosis

cc: Drs. Darley
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